A Dissertation on

NON ALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE IN DIABETIC PATIENTS

Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI

in partial fulfillment of the regulations
for the award of the degree of

M.D BRANCH - I

GENERAL MEDICINE

GOVT.STANLEY MEDICAL COLLEGE & HOSPITAL

CHENNAI – TAMILNADU

MAY 2018

CERTIFICATE

This is to certify that this dissertation entitled **"NON ALCOHOLIC FATTY LIVER DISEASE FIBROSIS IN DIABETIC PATIENTS"** submitted **by DR.SINDHIYA JAYACHANDRAN** to the Tamilnadu Dr. M.G.R medical University is in partial fulfillment of the requirement of the award of **M.D DEGREE (BRANCH-I)** and is a bonafide research work carried out by her under direct supervision and guidance.

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DECLARATION

I solemnly declare that the dissertation entitled **"NON ALCOHOLIC FATTY LIVER DISEASE FIBROSIS IN DIABETIC PATIENTS"**was done by me at the Government Stanley Medical College and Hospital during **MARCH-SEPTEMBER 2017** under the guidance and supervision of **Prof.Dr.P.VASANTHI. M.D.** The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfillment of requirement for the award of M.D. Degree (Branch-I) in General Medicine.

Place:

Date :

DR.SINDHIYA JAYACHANDRAN

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INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Non Alcoholic Fatty liver disease fibrosis score in Diabetic Patients.

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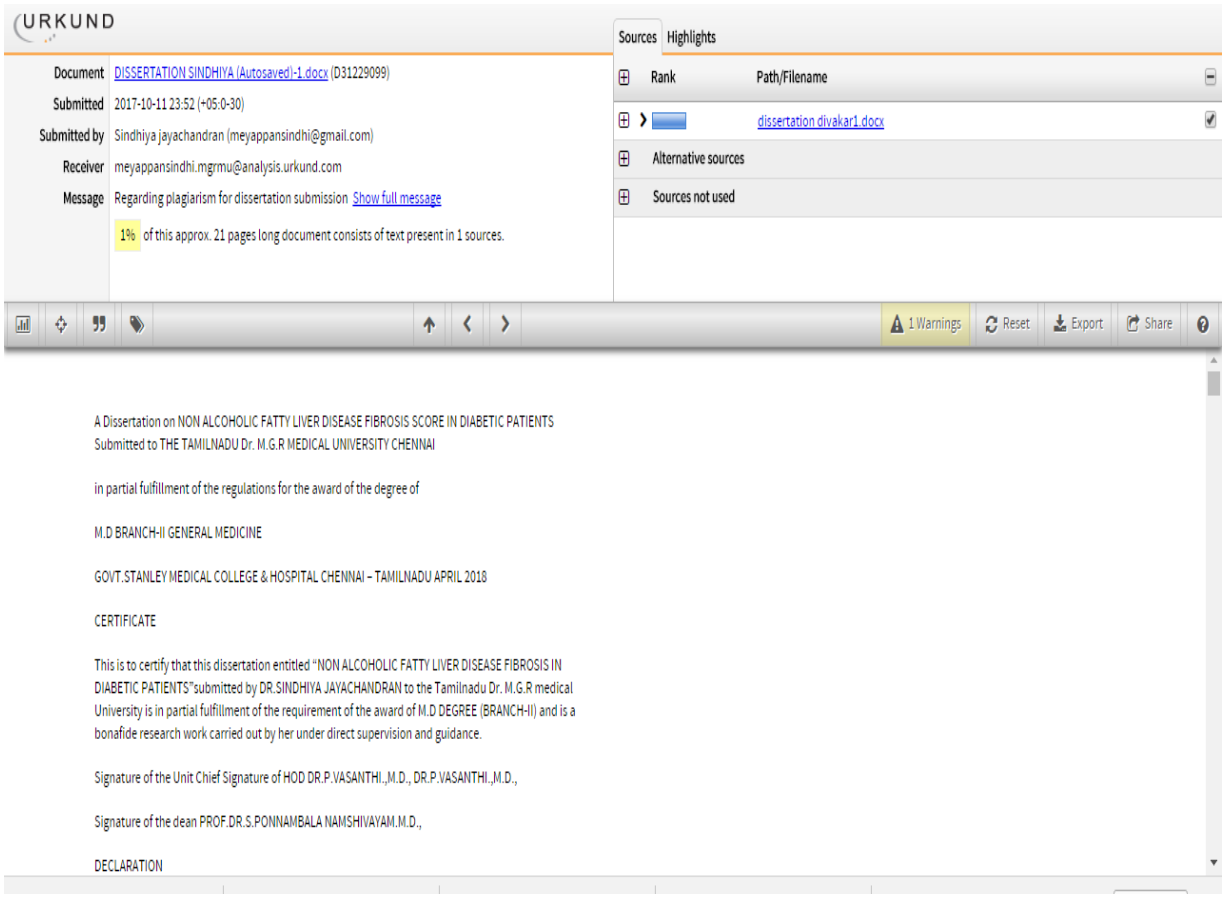

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Signature of the dean PROF.DR.S.PONNAMBALA NAMSHIVAYAM.M.D.,

DECLARATION

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ANNEXURE

INTRODUCTION

1. INTRODUCTION

Non alcoholic fatty liver disease is increasingly being recognised as a major cause of liver related morbidity and mortality, because of its potential to progress to cirrhosis and liver failure. NAFLD is deposition of fat in the liver of a non-alcoholic subject, a condition which may progress to end stage liver disease. (1)

NAFLD is an extremely common liver disease in the United States (USA), affecting approximately 20% of the adult population. In different countries, its prevalence is 10-24% of the general population. Amongst the obese persons, the prevalence rises to 57-74% and 25-75% among obese diabetics. Accordingly, NASH is considered as the third commonest cause of liver disease after alcohol abuse and hepatitis C.Patients with Diabetes mellitus have an increased risk of developing the spectrum of non alcoholic fatty liver disease (NAFLD) manifestations ranging from simple steatosis, non alcoholic steatohepatitis, hepatic fibrosis, cirrhosis and liver failure. Furthermore Diabetes mellitus with NAFLD have three times high mortality compared to non-diabetic NAFLD.

NAFLD fibrosis score is non invasive predictive score for hepatic fibrosis which includes six parameters and categorised into three groups based on the scores.F0-F2= <-1.455, Intermediate= -1.455-0.675,F3-F4=>0.675.

AIM OF THE STUDY

2.AIM OF THE STUDY

1. To categorize the Type 2 diabetic patients into four groups-obese, non-obese, ultrasonographic presence and absence of hepatic steatosis.

2. To analyse the risk of hepatic fibrosis in these patients using NAFLD FIBROSIS SCORE.

3.To correlate the stage of fibrosis by fibro scan in group of patients with high NAFLD score.

REVIEW OF LITERATURE

3.REVIEW OF LITERATURE

Nonalcoholic fatty liver disease (NAFLD) is a broader term with a spectrum including patients with simple steatosis, steatohepatitis that can progress to cirrhosis liver and even hepatocellular carcinoma.(1)(2). In 1980, Ludwig et al(3) described the term NASH as a form of liver injury that was histologically consistent with alcoholic hepatitis but occurred in obese, diabetic females, who denied alcohol use. The prevalence of NAFLD and NASH in the general population is estimated to be between 10%-24% and between 1%- 5%, respectively. There is a direct correlation between body mass index (BMI) and prevalence and severity of NAFLD. The prevalence of NAFLD increases to 57.5% to 74% in obese persons and 90% in morbidly obese persons.(4)(5)(6).In India prevalence of NAFLD is around 9% to 32% of general population.(7)(8)

NAFLD not only affects the liver, it is a multisystem disease affecting extra-hepatic organs and regulatory pathways. It increases risk of type 2 diabetes mellitus, cardiovascular and cardiac diseases, chronic kidney disease and causal link in sleep apnea, colorectal cancers, osteoporosis, psoriasis and various endocrinopathies like polycystic ovary syndrome.

Most patients with NAFLD are asymptomatic and may have elevation of liver enzymes which is noted incidentally in biochemical investigations. Alanine amino transferase and as partate amino transferase are usually elevated, but these levels do not reliably correlate with hepatic injury, inflammation or cirrhosis in NAFLD.

3.1.NATURAL HISTORY OF NAFLD:

About 90% of Patients with **NAFLD** have simple steatosis and therefore no increase in mortality (9)(10), approximately 10-30% patients have NASH (Non Alcoholic Steatohepatitis) which is associated with hepatocellular injury and inflammation.25-40% of patients with NASH will develop progressive fibrosis and cirrhosis and end stage liver disease.(11)(12)(13).Recent data states that 28% of patients have progression on histological examination, 59% have no change, and 13% may have improvement. Matteoni et alretrospectively determined the histological and/or clinical outcome of 98 patients with the whole spectrum of NAFLD from simple steatosis through NASH to cirrhosis.

After a median 8-year follow up, 25% of individuals with evidence of hepatocyte necrosis with or without Mallory's hyaline or fibrosis, either already had cirrhosis on index biopsy or progressed to cirrhosis. This compared with only 3.4%of patients with simple steatosis with or

without non-specific inflammatory changes. These observations indicate that NAFLD patients without NASH have a benign prognosis.(14)

The development of cirrhosis due to NASH is associated with a poor prognosis. 10-year mortality rate is 20% for subjects with Child-Pugh A disease and 45% will decompensate within 10 years of diagnosis.(15)Patients with cirrhosis due to NASH are at significant risk of developing hepatocellular carcinoma.(16)

3.2.RISK FACTORS OF NAFLD:

3.2.1.AGE:

Higher risk is associated with increasing age of the patient.

3.2.2.METABOLIC SYNDROME:

Metabolic syndrome is independent predictor of fibrosis.70-90% of patients with NAFLD have metabolic syndrome. Insulin resistance is a key mediator between NAFLD and metabolic syndrome (17).Any three of the following features is diagnosed as metabolic syndrome.

a. Central obesity – Waist circumference >94cm for men and >80cm for women.
b. Impaired fasting glucose - >5.6 mmol/L or on treatment.
c. Hypertriglyceridemia - >1.7 mmol/l or on treatment

d. Low HDL cholesterol - <1.0 mmol/l for men or on treatment
   <1.3 mmol/l for women or on treatment
e. Hypertension - >135/85 mm Hg or on treatmernt

3.2.3.GENDER:

NAFLD is more common in men compared to women, but progression to advanced fibrosis is higher in women compared to men.(18)(19)

3.2.4.ETHNICITY:

NAFLD risk is higher in Hispanics population and lowe in black population.(20)

3.2.5.DIETARY FACTORS:

Diet containing high cholesterol and saturated fats, high fructose intake, low carbohydrates increases the risk of NAFLD(21)(22).

Caffiene may be protective in some patients.(23)

3.2.6.OBSTRUCTIVE SLEEP APNOEA:

It increases the risk of NAFLD.(24)(25)

3.2.7. GENETIC FACTORS:

Patatin –like phospholipase domain- containing 3 (PNPLA3). (25)(26)(27) PNPLA3 lysophosphatidic acid acyltransferase activity could also contribute to altered plasma triacylglycerol composition and concentration.

3.2.8.NUTRITIONAL FACTORS:

Obesity, rapid weight loss, total parenteral nutrition, prolonged starvation are attributed as causal factors in NAFLD.

3.2.9.DRUGS:

Corticosteroids, Amiodarone, Bleomycine, Tetracycline, Methotrexate, Perhexiline, Diltiazem, nifedipine , Tamoxiphen.

3.2.10.CHEMICALS:

Hydrocarbons and yellow phosphorous are associated with fatty liver.

3.2.112.SURGERY:

Surgeries like Jejunoileal bypass,extensive small bowel loss, gastropexy are associated with fatty liver.

3.3.ETIOPATHOGENESIS OF NAFLD/NASH:

The pathogenesis of the NASH is not completely understood.The conditions associated with NAFLD include nutritional abnormalities, metabolic disorders, drugs, chemicals and surgery as mentioned above.Initially there is steatosis which later, after a series of events, may progress on to inflammation and fibrosis and finally to cirrhosis and end stage liver disease.(28)(29)(30) NASH may be considered as a two hit process, first hit is accumulation of the fat and the second hit is hepatocellular injury in the fatty liver .(30)The first hit of steatosis occurs because of the imbalance between the fatty acid uptake, its oxidation, esterification and export as very low-density lipoprotein (VLDL) from the hepatocytes. Insulin resistance is the most important key factor(28)((30)(31)which leads to increase in lipolysis and increased uptake of fatty acids by hepatocytes.

Hyperinsulinemia which occurs as result of insulin resistance increases the intrahepatocytic fatty acids by increasing the glycolysis and decreasing the apolipoprotein B-100 and resulting in decreased export as VLDL. The end result is the increase in fatty acids and triglycerides in the hepatocytes leading to steatosis or fatty liver.

The free fatty acids in the hepatocytes acts as reactive oxygen species and increases the mitochondrial β-oxidation and cytochrome P-450 4A and cytochrome P450 2E1 levels.The mitochondrial oxidative stress leads to the second hit from steatosis to steatohepatitis and fibrosis by three main mechanisms, namely (i) lipid peroxidation, (ii) cytokine induction, and (iii) Faslig and induction.(28)(30)

(i). Lipid peroxidation causes oxidative destruction of polyunsaturated fatty acids of cellular membranes. The cytotoxic products which are released due to lipid peroxidation impair cellular functions including nucleotide and protein synthesis leading to cell death, formation of Mallory hyaline, promoting tissue inflammation, activation of stellate cells and collagen synthesis.(28)

(ii). Cytokines like IL-1, IL-6 IL-8 and tumor necrosis factor-α (TNF-α) plays an important role in the pathogenesis of liver injury in patients with NASH.(31)

IL-1, IL-6, and IL-8 are pro-inflammatory cytokines and IL-10 and IL-12 are anti-inflammatory cytokines. TNF-α, TGF-β, interleukin-8 and cause chemotaxis, formation of Mallory hyaline and synthesis of collagen by activated stellate cells.

TNF–αdownregulates insulin-induced phosphorylation of insulin receptor substrate 1 and reduces the expression of the insulin-dependent glucose transport molecule Glut 4 and thus contributes towards insulin resistance which is thought to be the major mechanism in the pathogenesis of NASH.(31)(32)

TNF-α is derived from adipose tissue in the absence of active infections or inflammatory conditions. Plasma levels of TNF-αalso correlates with body fat mass and is associated with insulin resistance. (37) TNF-α knockout mouse also fails to develop insulin resistance after induction of obesity suggests its crucial role in the pathogenesis of insulin resistance.(38)The oxidative stress leads to the IkKβ activation and release of TNF- α and insulin resistance, which ultimately leads to steatohepatitis.

(iii). Finally the expression of Fas ligand due to oxidative stress leads to fractional killing by interaction with Fas on other hepatocytes.

Other factors that are involved in the pathogenesis of NASH include serum and liver iron,(33)(34)leptin,(35) bacterial overgrowth, (36)(37)(38) Saturation of mitochondrial β-oxidation leads to peroxisomal oxidation and generation of hydrogen peroxide, which in the

presence of increased iron is converted to hydroxyl radicals, thus adding to the oxidative stress and further injury.(39)

Leptin, a product of obesity gene regulates the food intake and body composition through a central feed back mechanism and is proposed to be a key pathophysiological factor for obesity. Leptin leads to hepatic steatosis by promoting insulin resistance or by modulating insulin signaling in hepatocytes.(34)

Bacterial overgrowth in the gut can cause liver injury by causing endotoxemia and release of cytokines. The mechanisms by which intestinal bacteria may increase hepatic oxidative stress include increased endogenous production of ethanol and by direct activation of inflammatory cytokines in luminalepithelial cells, and liver macrophages or both .(35)

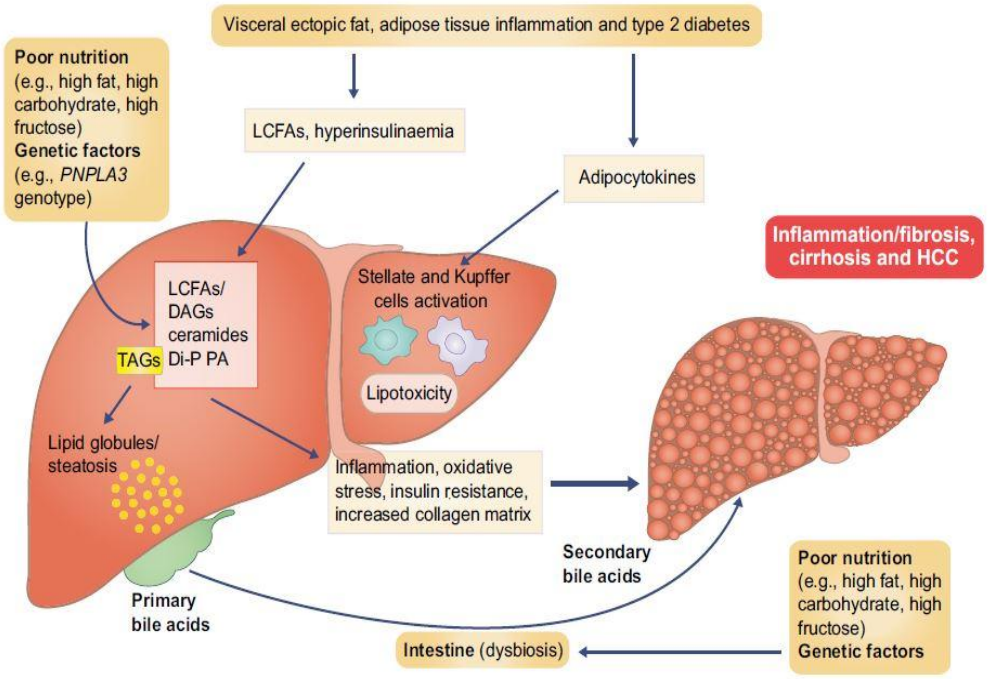


FIG 1: The factors like visceral ectopic fat accumulation, adipose tissue inflammation, type 2 diabetes and intestinal dysbiosis which promote development of progressive liver disease in NAFLD.(Non Alcoholic Fatty Liver Disease)

3.4.NAFLD AND DIABETES MELLITUS:

When imbalance occurs between energy intake and energy expenditure, or an intrinsic problem with storing excess energy as lipid (triacylglycerol) in adipose tissue depots, lipid occurs in other organs throughout the body. Ectopic fat accumulation is defined as lipd accumulation in tissues, organs not designed to accumulate e.g., liver or omentum other than adipose tissue.(40)

NAFLD is an ectopic fat accumulation which is associated with increased secretion of hepatokines (41), increased gluconeogenesis, decreased glycogen synthesis and inhibition of insulin signaling (42)(43). Adipose tissue inflammation is crucial in NAFLD pathogenesis and evidence suggesting that dysbiosis of the gut microbiota plays a major key role in development and progression of NAFLD. This is mailnly because of the increased intestinal absorption of bacterial products, such as short-chain fatty acids (e.g., butyrate, propionate and acetate), lipopolysaccharide and endotoxins.

Mechanisms involved in the pathogenesis of insulin resistance and inflammation in NAFLD is explained briefly.Although obesity is strongly associated with hepatic steatosis,excess body fat accumulation is not ‘sine qua non’ for developing NAFLD. In fact, patients with lipodystrophy have marked insulin resistance and commonly develop hepatic steatosis

and T2DM, strongly suggesting that it is not body fat mass per se that is important, but it is adipose tissue dysfunction that is a key contributor to the pathogenesis of NAFLD (46).

Specifically, increased free fatty acid (FFA) fluxes from the adipose tissue pool increase the availability of long-chain fatty acyl-CoAs for hepatic lipid accumulation, particularly in physically inactive individuals(44), and evidence is accumulating that hepatic lipid accumulation is capable of causing hepatic/peripheral insulin resistance and promoting hepatic inflammation (40)(44).Expansion of peripheral adipose depots provides buffering capacity that may protect the liver from the excessive FFA fluxes that promote hepatic lipid accumulation. Within hepatocytes, long-chain fatty acids are esterified with glycerol-3-phosphateto form mono-acylglycerols, di-acylglycerols and tri-acylglycerols.

Lipid synthesis is very important in causing ‘resistance’within the hepatic insulin signaling pathway (47), promoting hepatic inflammation (48) and increasing risk ofprogressive liver disease that occurs with NASH. In the liver ceramides can accumulate into the cells via three main routes: 1) the hydrolysis of the membrane phospholipid sphingomyelin, which is coordinated by the enzyme sphingomyelinase; 2) de novo synthesis from long chain fatty acids such as palmitate and

serine; and 3) a ‘salvage’ pathway that utilizes sphingosine and forms ceramide (54)(55). Ceramide plays an important role in causing insulin resistance.(55)

Hepatic lipids that are not esterified also induce endoplasmic reticulum stress, leading to the activation of c-Jun N-terminal kinases and NF-jB (55),which are two major regulators of inflammatory pathways that also inhibit phosphorylation of insulin receptor substrate-1 (IRS-1) (56), potentially aggravating hepatic insulin resistance and increasing intra-hepatic cytokine production . Synthesis of lipids such as di acyl glycerol (DAGs) is intimately related to inflammatory pathways, and DAGs may also contribute to hepatic production of inflammatory cytokines [e.g.,tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6)], and procoagulant factors [e.g., factor VIII, plasminogen activator inhibitor-1 (PAI-1)].

Intestinal microbiota dysbiosis may affect other hepatic lipid pathways, such as those involving bile acid metabolism,consequently increasing hepatic inflammation and fibrosis,and resulting in an increased risk of developing cirrhosis and HCC.

Till date, it is unclear whether improvements in NAFLD may ameliorate risk of T2DM or improve glycaemic control in people with

NAFLD who have developed T2DM, but it is plausible that resolution of liver fat and improvements in liver lipid metabolism might modify the risk of T2DM via a liver-specific effect. Such a liver-specific effect could be mediated by alteration in the secretion of multiple hepatokines or inflammatory cytokines that influence risk of diabetes. In NAFLD, secretion of diabetogenic hepatokines, such as retinol binding protein (RB)-4, fetuin-A, fibroblast growth factor (FGF)-21; or inflammatory biomarkers such as C-reactive protein (CRP), TNF-a and IL-6 (57)may directly affect risk of incident T2DM by adversely affecting hepatic gluconeogenesis,glycogen synthesis and insulin signaling (58).

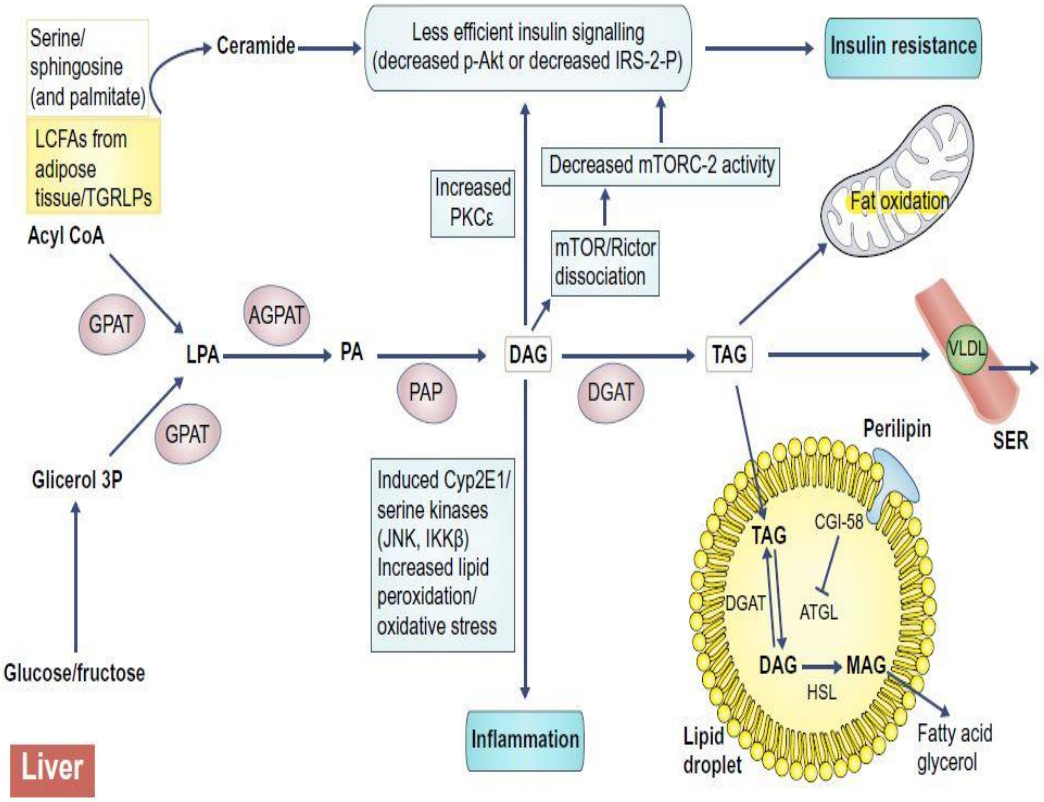


FIG 2 : Mechanism of insulin resisratance, adipose tissue inflammation and role of hepatokines, adipokines in NAFLD.

3.5.NAFLD AND METABOLIC SYNDROME:

Metabolic syndrome is characterized by the presence of insulin resistance in association with other metabolic abnormalities like obesity, diabetes, hypertriglyceridemia and hypertension. Common associations of NAFLD, such as hypertension, hyperuricemia, and polycystic ovary syndrome are also common to metabolic syndrome.

The chances of individual having NAFLD and NASH increase with increasing body weight, with 70-80% of obese individuals having NAFLD and 15-20% having NASH. Conversely 30-100% of NASH patients have obesity.

Truncal obesity is more commonly associated with NASH, also with causal link to diabetes and hypertension. In morbidly obese patients, the risk of liver disease progressively increases with the number of features of metabolic syndrome.(59)(60)Metabolic syndrome was present in 22% of Indian patients with NASH.(61)

3.6.NAFLD AND CARDIOVASCULAR DISEASES:

Non alcoholic fatty liver disease is associated with increased risk and morbidity for cardiovascular diseases and risk further increases in Type 2 diabetus mellitus. In addition pateints with non alcoholic steatohepatitis have further increased risk of cardiovascular diseases.

Myocardial metabolism is primarily affected in NAFLD. By cardiac magnetic resonance imaging (MRI), Perseghin et al. reported that nonobese, nondiabetic, normotensive, young individuals with NAFLD had impaired myocardial energy metabolism (i.e., a lower phosphocreatine/adenosine triphosphateratio, as measured by 31P-magnetic resonance spectroscopy and excessive fat accumulation in the epicardial area compared with control subjects without NAFLD. Interestingly, these myocardial metabolic alterations were detected despite normal left ventricular (LV) morphological features and systolic and diastolic functions (62). Lautamaki et al.(63)and Rijzewijk et al. (64)found that T2DM patients with higher intra-hepatic fat content on 1H-MRS had increasedmyocardial insulin resistance and decreased myocardial perfusion compared with those with lower intra-hepatic fat content, additionally, myocardial insulin resistance was more severe among those with higher intra-hepatic fat content , those with higher intra-hepatic fat content had significantly higher myocardial fat content.

Interestingly, in this study cardiac steatosis was astrong predictor of LV diastolic dysfunction.(65) NAFLD with increased liver transaminases is an independent risk factor for atrial fibrillation in the Framingham Heart Study cohort (66).

Asimilar link was found between elevated serum liver enzymes and AF risk was shown in a larger prospective community-based study of 9333 subjects with a follow up for 12 years (67). NAFLD is also independently linked with prolonged QTc interval which is a powerful predictor of ventricular arrhythmias and sudden cardiac death and the presence of progressive aortic valve sclerosis. All these factors contributes to increased cardiovascular risk in NAFLD patients.(68)(69)

3.7.NAFLD AND CHRONIC KIDNEY DISEASE:-

The prevalence of chronic kidney disease is increased among patients with non alcoholic fatty liver disease with or without diabetes mellitus. The estimated glomerulation filtration rate and overt proteinuria is measured in patients with chronic kidney disease.(70)The severity of NAFLD varied upon the stages of chronic kidney disease. The patients had fatty kidney and increased renal sinus fat volume caused structural and functional derangements in the kidneys.(71)

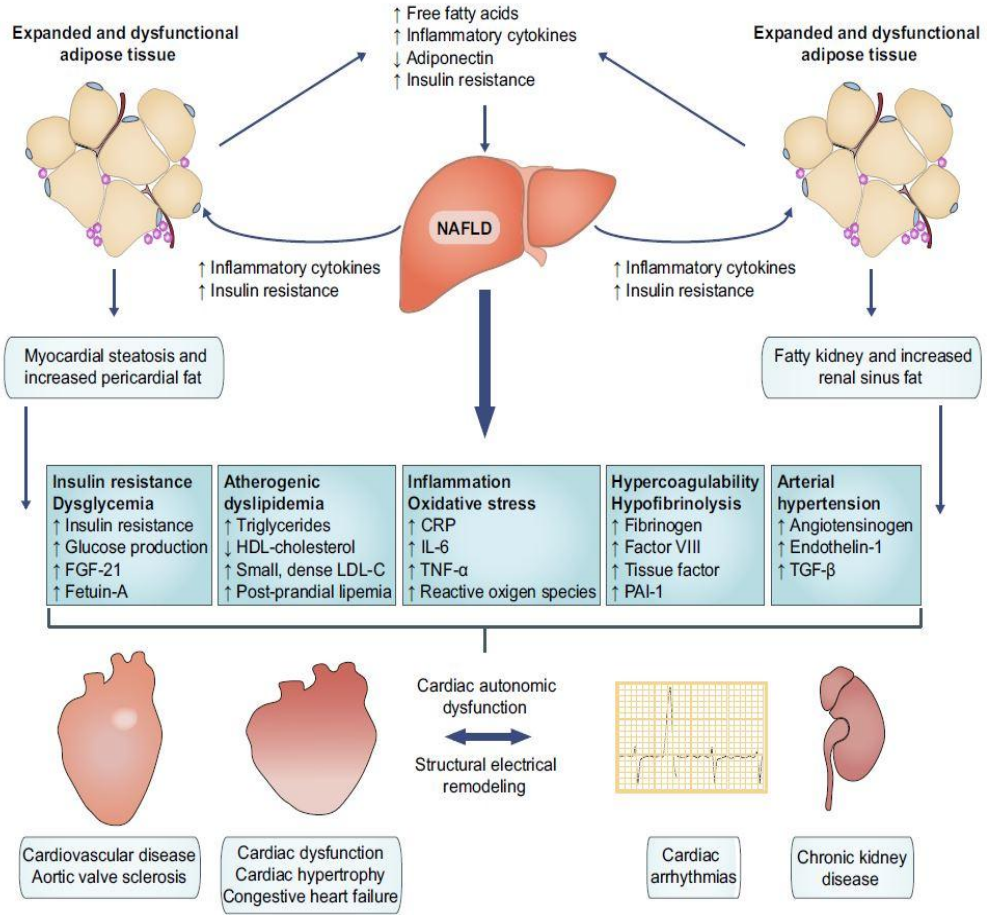


FIGURE 3: The link between NAFLD and cardiovascular and kidney structural and functional changes.

3.8. CLINICAL FEATURES:

1.SYMPTOMS:-

- Asymptomatic (30-40%)
- Right upper subcostal pain or discomfort (30-40%)
- Fatigue (<10%)
- Pedal edema
- Gastrointestinal bleeding
- Abdominal distension

2. SIGNS:-

- Normal examination
- Increased body mass index (BMI)
- Increased waist circumference (truncal obesity)
- Stigmata of chronic disease if cirrhosis is present.
- Lipomatosis/lipoatrophy /lipodystrophy
- Hepatomegaly (50-70%)
- Splenomegaly
- Ascites

3.9. INVESTIGATIONS:

3.9.1. BIOCHEMICAL :

i. Raised aspartate aminotransferase (AST) and alanine aminotransferase (ALT) - up to 4-5 times elevation

ii. Alkaline phosphatase - up to 2 times elevation

iii. AST/ALT - majority <1; >1 may indicate cirrhosis

iv. Bilirubin - elevated in late stage

v. Albumin - decreased in late stage

vi. Prothrombin time - prolonged in late stage

vii. Serum markers of iron overload - ~25% but do not indicate hemochromatosis.

viii. Anti-nuclear antibody - one-third

3.9.2. FIBROSIS SCORES:

1.NAFLD FIBROSIS SCORE:

Fibrosis staging is important in all patients with NAFLD to identify patients with advanced hepatic fibrosis at risk of liver-related complications. Hepatocellular dysfunction and portal hypertension result from advancing hepatic fibrosis. This can be noticed in blood investigations such as liver function tests (low albumin), full blood count (thrombocytopenia) and coagulation profile (prolonged prothrombin time). These tests give an indirect measure of fibrosis and act as non-

invasive markers of fibrosis as they are less cost and are performed in all patients with hepatic disease. With increasing hepatic fibrosis, the ALT typically falls and the AST remains stable or rises and as a result, the AAR (aspartate and alanine amino transferase ratio) increases and can be an useful simple method of identifying patients with advanced fibrosis. Previous studies identified a cut-off>1 for the AAR as a diagnostic test for cirrhosis. (72)(73)

2.BARD SCORE:

The BARD score is a simple test using thebody mass index>=28 – 1 point, AST/ALT ratio >=0.8 -2 points and presence of type 2diabetes mellitus – 1 point. The score ranges from 0 to 4 points. A score <2 has excellent negative predictive value of95–97%, which excludes advanced hepatic fibrosis.

However, in a typical NAFLD cohort, a large proportionof patients with mild disease have a score of ≥2because of diabetes limiting its utility in clinical practice.(74)

3.FIB-4 SCORE:

The FIB-4 score althoughderived in patients with HIV and HEPATITIS B coinfection, appears to be one of the most essential noninvasive tests for diagnosing advanced fibrosis inNAFLD. For stage

3–4 fibrosis, a score <1.3 has a90% NPV and a score >2.67 has an 80% PPV, with 72% of patients scoring below 1.3 or above 2..Other studies have proved that the FIB-4 score is considered slightly better than other non-invasive tests in diagnosing advanced fibrosis in NAFLD, including in subjects with normal range ALT levels.(75)

4.CK-18:

Levels of cytokeratin-18 (CK-18) fragments correlate with the magnitude of Hepatocyte apoptosis and predict the presence of NASH(non alcoholic steatohepatitis).Cytokeratins are proteins of keratin containing intermediate filaments found in intracytoplasmic cytoskeleton of epithelial tissue. Mallory body composed of abnormally phosphorylated cross linked keratins like cytokeratin 8 and 18.

5.HAIR SCORE:-

1. Alanine transaminase (ALT) > 40 IU/l
2. Insulin resistance (IR) index > 5
3. Hypertension

Presence of 2 or all 3 factors predict NASH.

6. **BAAT SCORE:-**

1. Age > 50 yrs.

2. Body mass index (BMI) > 28 kg/m2.

3. Triglyceride> 1.7 mmol/l.

4. Alanine aminotransferase (ALT)> 2-fold rise.

Presence of none or only 1 factor rules out the possibility of fibrosis or cirrhosis.

7.OTHER NON INVASIVE TESTS:

The Enhanced Liver Fibrosis (ELF) test is a commercialpanel of markers of matrix turnover: tissue inhibitor of matrix metalloproteinase 1 (TIMP1), hyaluronic acid and PIIINP.(76) Fibrotest (FT) is a commercial tool of biochemical markers of fibrosis that is prevalently used in France. In NAFLD, FT can diagnose advanced hepatic fibrosis withmodest accuracy .Using a FT cut-off of 0.30 gives a 90% NPV for advanced fibrosis (sensitivity 77%), and a FT cut-off of 0.70 had a 73% PPV for advanced fibrosis (specificity 98%).Other scores include Palekar's score,Gholam score,Nippon score and BAAT score.(77)

3.9.3.IMAGING:

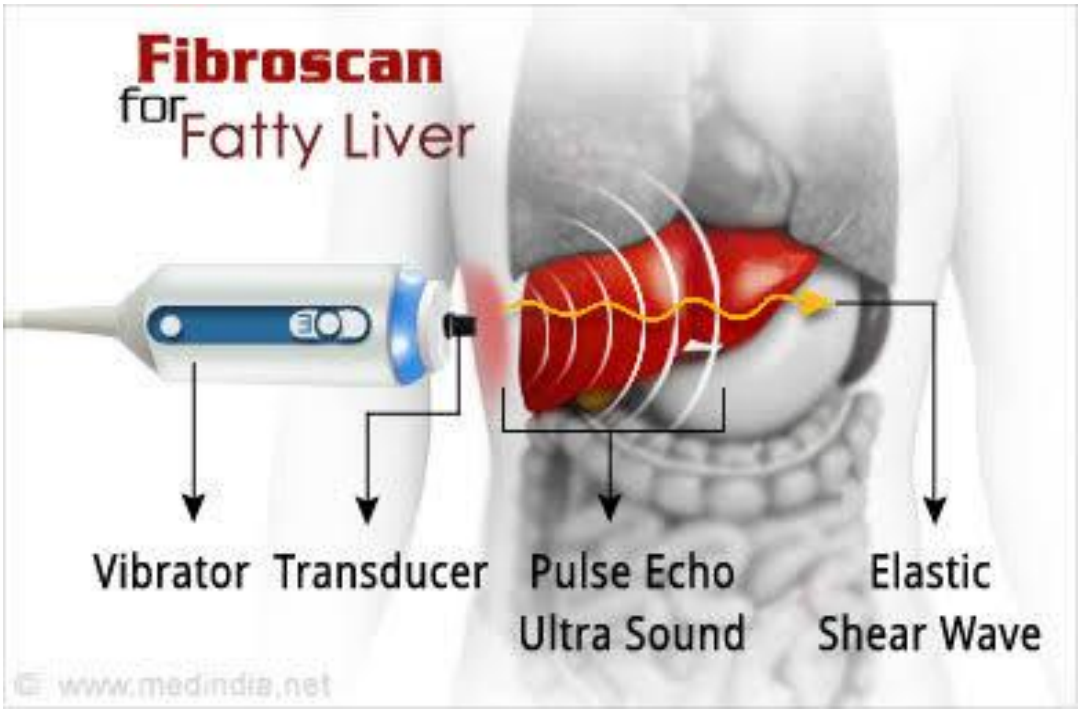
- **Ultrasound :**

Findings of hepatic steatosis in ultrasound are increased echogenicity and coarsened echotexture of the .If steatohepatitis has progressed to cirrhosis, a nodular liver surface may be present in addition to other fibrotic changes.

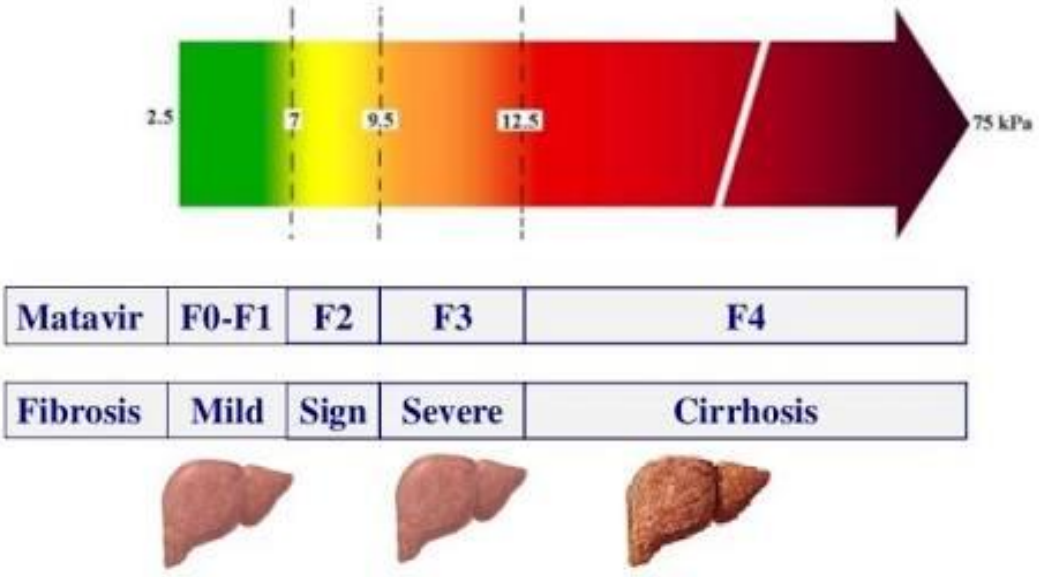
- **Fibro scan:-**

Fibrotic livers have less elasticity due to the fibrous tissue deposition in the hepatic parenchyma. TE (Fibroscan) gives a ‘liver stiffness measurement’(LSM) using pulsed-echo ultrasound as a surrogate marker of fibrosis. The LSM correlates well with the degree of liver fibrosis in a wide range of liver diseases, including NAFLD.(78)

However, there are multiple drawbacks in using TE in NAFLD. Invalid results appear in older patients (>52 years) and those with central obesity (BMI >35 kg/m2) or type 2 diabetes. The Fibroscan XL probe has been developed for obese patients but is associated with fewer LSM failures.



Liver stiffness cut-offs in chronic liver diseases



- **Computed tomography/Magnetic resonance imaging**

A. CT scan findings in NAFLD:

- Picking up of focal areas of fatty infiltration.
- Mean CT Hounsfield unit in liver(diffuse hypoattenuation) less than that inspleen helps in diagnosis.

B. MRI findings in NAFLD:

- Phase contrast imaging gives adequate information about fatty infiltration of liver giving very good quantitativeassessment of status of disease.
- Useful for excluding fatty infiltration.
- On T1-weighted images, there is loss of intensity in focal areas of deposition of fat. So,in early stage of disease ,small lesions are readily identifiedon MRI
- It is more sensitive and specific compared to USG or CTscan, but is expensive.

C. Radionuclide scanning (scintigraphy) studies:

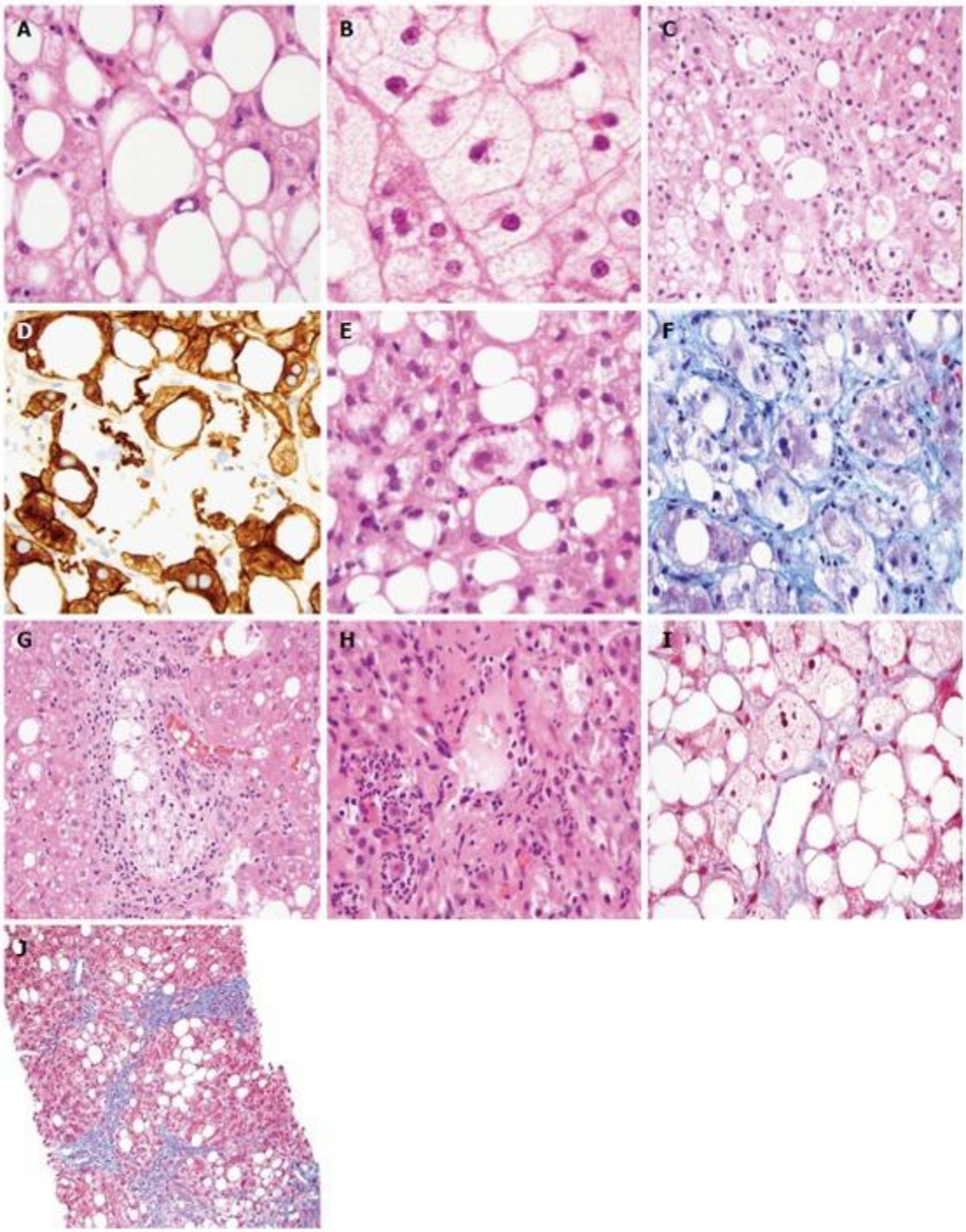
- With technetium-99m sulphur colloid scanning, focal areas of deposition of fat appear as fillingdefects.
- Radio-xenon has a very high affinity for fat and itremains bound to fat and retained in fat. This gives qualitative as well as quantitative assessment offat deposition in liver.

- **ARFI:**

The non-invasive assessment of hepatic fibrosis is acoustic radiation force impulse (ARFI). This technique uses conventionalB-mode ultrasonography to generate anultrasonic pulse and measurement of the response of the livertissue as shear wave velocity. The degree of hepatic fibrosis correlates with median velocity measured by ARFI.(79)

3.9.4.LIVER BIOPSY:

Performing a liver biopsy on every patient with suspected NAFLD remains a controversial area in practice, and clearly is not a practical consideration as a "screening" tool. The general indications for performing a liver biopsy in patients with NAFLD are to confirm or exclude the diagnosis, diagnose other liver diseases, and to determine amounts of damage to the liver for treatment and prognosis. The last includes necroinflammatory activity, which is potentially reversible, and collagen deposition with varying degrees of remodeling, which is potentially less reversible. The major limitation of liver biopsy is the invasive nature of the procedure.(80) Though considered "minimal", liver biopsy is an invasive procedure and can have complications even in the ideal clinical conditions, including pain, minor and major bleeding (0.3%).(81)



A: Mixed large and small droplet steatosis, single droplet, with nucleus pushed to one side,

B: Microvesicular steatosis, nuclei in the center with foamy cytoplasm, and mega mitochondria

C: Ballooned hepatocytes with flocculent cytoplasm.

D: Loss of cytoplasmic expression of keratin 8/18 in ballooned hepatocytes,

E: Mallory-Denk body

F: Mallory-Denk body in blue-green color and dense perisinusoidal fibrosis.

G: Portal lipogranuloma.

H: Mallory-Denk bodies andsatellitosis.

I: Delicate perisinusoidal fibrosis.

J: Bridging fibrosis.

TREATMENT OF NON ALCOHOLIC FATTY LIVER DISEASE:

Treatment is aimed at correcting the risk factors for NAFLD, such as, medical control of hyperglycemia, and use of lipidlowering agents for hypertriglyceridemia, and lifestyle modification and pharmacological agents to improve insulin sensitivity.

INSULIN SENSITIZERS:-

Thiazolidinediones are a class of drugs that stimulate peroxisome proliferator activated receptors (PPAR).An insulin-sensitizing medication, troglitazone (a thiazolidinedione) is used.

LIPID LOWERING AGENTS:

Hypertriglyceridemia is associated with NAFLD. Clofibrate and gemfibrozil can be used.

PHARMACOLGICAL THERAPY OFFERING HEPATOCYTE PROTECTION:

Ursodeoxycholic acid (UDCA), and the anti-oxidants, betaine and vitamin E, have peer-reviewed published data.Other drugs, e.g., lecithin, *β*-carotene, selenium, and *N*acetylcysteine.

UDCA:-

This hydrophilic bile acid with hepatoprotective properties was first evaluated in a pilot study, where it was associated with both improved liver enzyme levels and a decrease in hepatic steatosis.

Vitamin E (*α*-Tocopherol):-

The observation that vitamin E decreases oxidative stress provides a rationale For its use in patients with NASH. One uncontrolled trial in children with NASH showed that supplementation with vitamin E (400 to 1200 IU daily) was associated with a significant decline in serum aminotransferases.

There was a significant improvement in fibrosis scores in the NASH patients receiving vitamins compared to baseline but no improvement in necroinflammation or ALT.

Betaine:-

Betaine, a normal component of the metaboliccycle of methionine, is a precursor of *S*-adenosylmethionine, a hepatoprotective factor.

Liver Transplantationis the choice of treatment in end stage liver disease.

MATERIALS AND METHODS

4.MATERIALS AND METHODS

This study was carried out in Govt Stanley Medical college Hospital, Chennai. This is a facility based observational study involved the patients who attended medicine and diabetology outpatient departments and as well as inpatients during the study period of March 2017-September 2017.

STUDY DESIGN:OBSERVATIONAL STUDY

DATE OF APPROVAL BY ETHICAL COMMITTEE:FEBRUARY 2017

PLACE OF STUDY:

DEPARTMENT OF INTERNAL MEDICINE,GOVERNMENT STANLEY MEDICAL GENERAL HOSPITAL,CHENNAI.

SELECTION OF CASES:

Diabetic outpatients and inpatients attending our instituite.

SAMPLE SIZE:

A total of 100 patients of diabetes mellitus who attended the outpatients department and admitted in medicine wards.

4.1 .INCLUSION CRITERIA:

1.All patients diagnosed as Type 2 Diabetes Mellitus by WHO criteria.

2.Age more than 18 years.

4.2.EXCLUSION CRITERIA:

1.Patients less than 18 years and more than 85 years.

2.Patients with history of alcohol intake more than 30 grams/day in males and more than 20 grams/day in females.

3.Patients with history of jaundice,Hepatitis B and C infection.

4.Patients with history of following drug intake such as steroids, synthetic Oestrogens,calcium channel blockers, amiodarone, valproic acid, heparin, antiviral agents.

4.3.METHODOLOGY:

Patients were made to understand in their local language and informed consent was obtained before collecting data and subjecting to investigations.

Patients were divided into four groups -obese group and non obese group according to WHOBMI criteria.BMI calculated by Quetelet index – Weight in kilograms / height in m^{2}·Ultrasonographic presence and absence of hepatic fibrosis.

- OBESE GROUP- BMI > 30kg/m^2
- NON OBESE GROUP – BMI <29.9 kg/$m^{2.}$

ASSESMENT OF PARAMETERS:

1.Age

2.Diabetes mellitus

3.Body mass index (BMI)

4.Aspartate aminotransferase level.

5.Alanine aminotransferase level.

6.Platelet count.

FORMULA OF NAFLD FIBROSIS SCORE:

-1.675+ 0.037 * AGE (years) +0.094 * BMI (kg/m^2) +1.13 * IFG/ DIABETES (yes =1,no=0) +0.99 * AST/ALT ratio - 0.013 * platelet (* 10^9 /l) -0.66 * albumin (g/dl).

EXPLANATION OF RESULT:

- NAFLD SCORE <-1-455 = F0 –F2 (LOW RISK)
- NAFLD SCORE -1.455- 0.675 = indeterminate score
- NAFLD SCORE >0.675 = F3- F4. (HIGH RISK)

OBSERVATION &

CALCULATION

5.OBSERVATION

100patients of Type 2 diabetes mellitus who attended general medicine and diabetology outpatient and inpatient departments in government stanley medical college during the period of march 2017 to september 2017 was studied and data collected and interpreted.

5.1.PATIENT CHARACTERISTICS:

5.1.1.PATIENT PROFILE:

Out of 100 patients,40 patients were male and 60 patients were females and patients were grouped into obese, non-obese, ultrasonographic presence of hepatic steatosis and ultrasonographic absence of hepatic steatosis.

Out of 100 patients, 57 patients (57%) were in obese group and 43 patients (43%)in non- obese group.

34 patients (59.6%) had ultrasonographic evidence of hepatic steatosis in the obese group.3 patients (6.9%) had ultrasonographic evidence of hepatic steatosis in non obese group.

23 patients (40.4%) had no ultrasonographic evidence of hepatic steatosis in obese group. 40 patients (93%) had no ultrasonographic evidence of hepatic steatosis in non-obese group.

5.2.PARAMETERS STUDIED:

5.2.1.NAFLD FIBROSIS SCORE:

Non alcoholic fatty liver disease fibrosis score was applied to all patients in both obese and non obese group and categorised into high risk, intermediate risk and low risk.

Accordingly 20 patients(35%) had high risk in obese group, 1 patient (0.2%) had high risk in non obese group.

21 patients (36%) had intermediate risk in obese group and 6 patients (13.9%) had intermediate risk in non obese group.

16 patients (28%) had low risk in obese group and 36 patients (83.7%) had low risk in non obese group.

5.2.2.FIBRO SCAN:

Non invasive fibroscan/ elastography was done to calculate the liver stiffness in patients with non alcoholic fatty liver disease and high NAFLD score.

Accordingly 20 patients of obese group had high risk of hepatic steatosis and fibro scan was done for the patients.

4 patients (20 %) had F0-F1 stage of fibrosis in fibro scan(according to METAVIR staging)

13 patients (65%) had F2-F3 stage of fibrosis.

3 patients (15%) had F4 stage of fibrosis.

TABLE 1: AGE RANGE OF STUDY POPULATION

Agerange

	Frequency	Percent
Upto 35 yrs	6	6.0
36 - 45 yrs	27	27.0
46 - 55 yrs	32	32.0
56 - 65 yrs	26	26.0
Above 65 yrs	9	9.0
Total	100	100.0

TABLE 2: STATISTICS OF AGE

AGE

N	Valid	100
	Mean	50.83
	Median	50.00
	Std. Deviation	10.431
	Range	48
	Minimum	26
	Maximum	74

FIGURE 1: PIE CHART REPRESENTING THE PERCENTAGE OF OBESE AND NON OBESE GROUP IN STUDY POPULATION

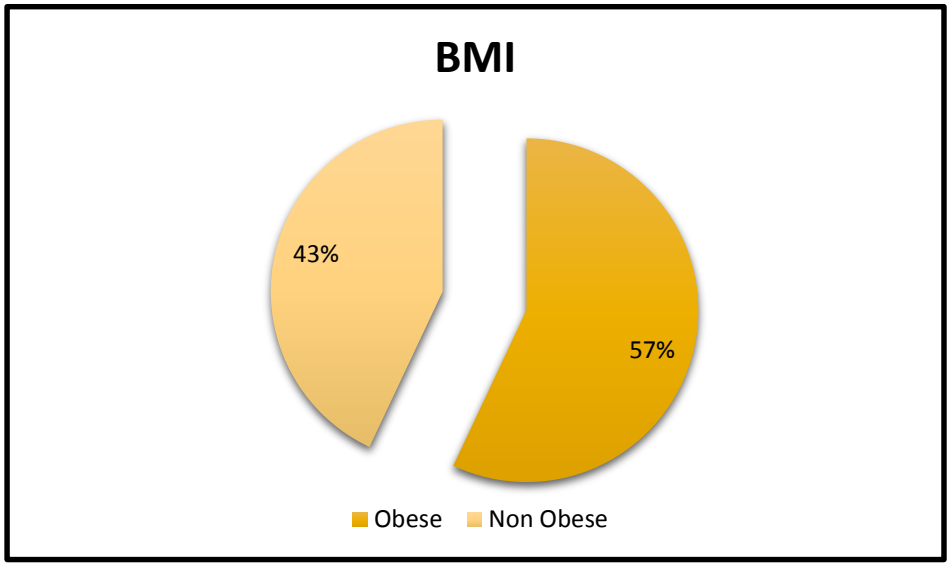


FIGURE 2: PERCENTAGE OF STUDY POPULATION WITH USG EVIDENCE OF FATTYLIVER AND NO FATTY LIVER

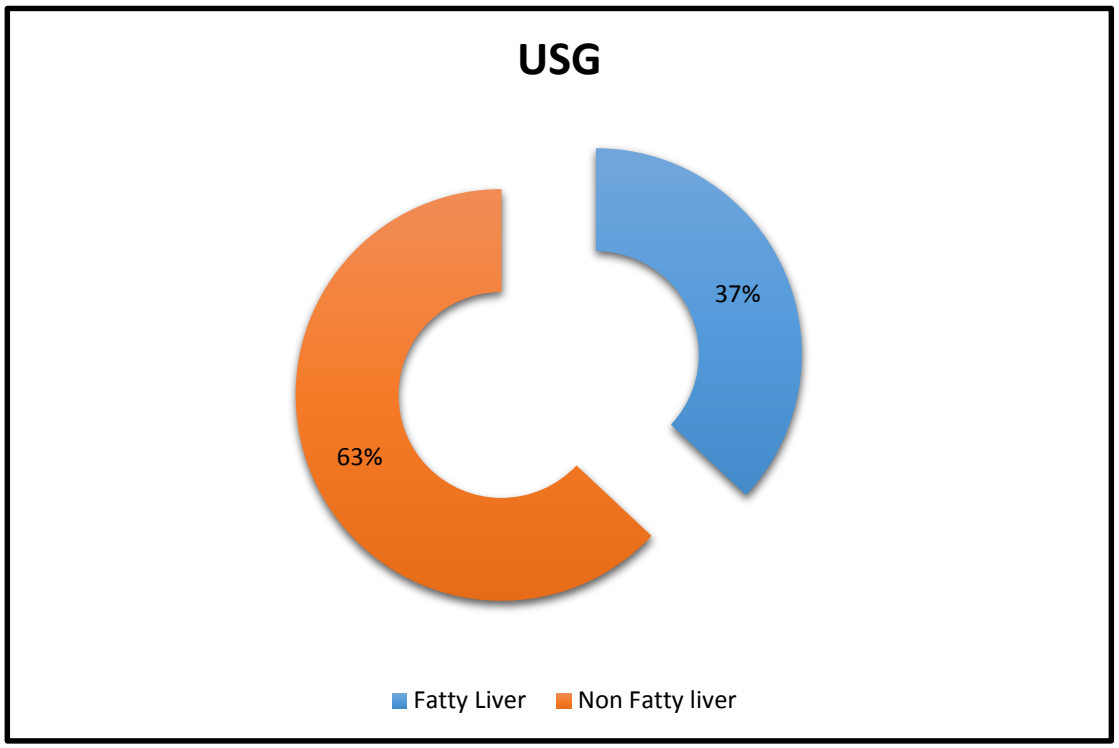


FIGURE 3: PERCENTAGE OF STUDY POPULATION HAVING EVIDENCE OF FATTY LIVER IN BOTH GROUPS.

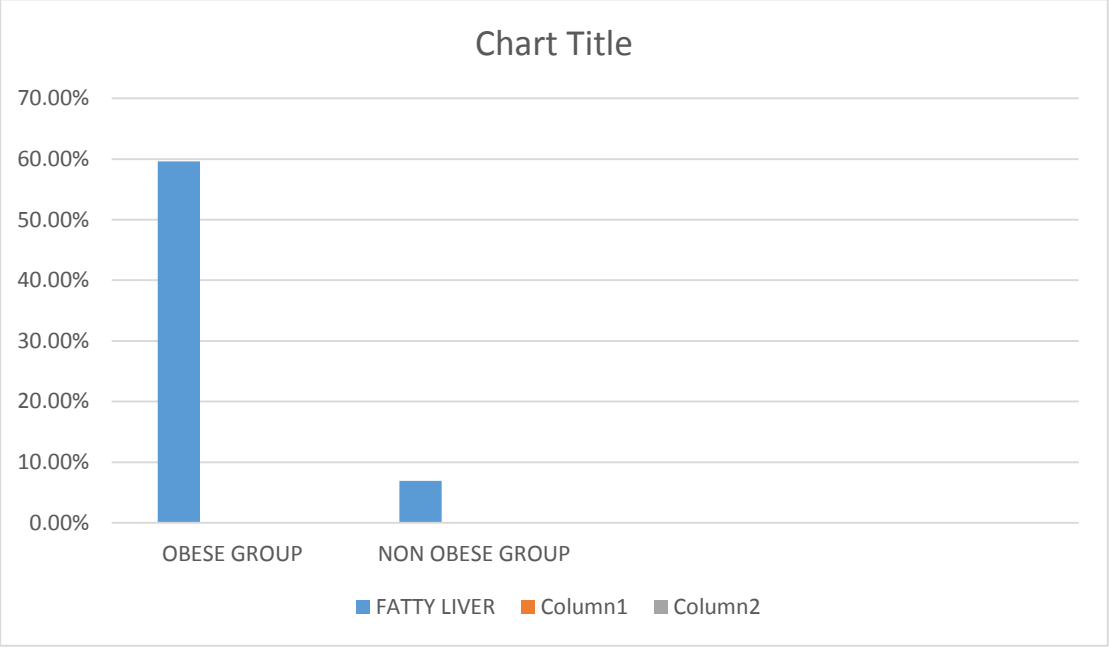


FIGURE 4: PERCENTAGE OF POPULATION WITH NO EVIDENCE OF HEPATIC STEATOSIS IN ULTRASONOGRAPHY

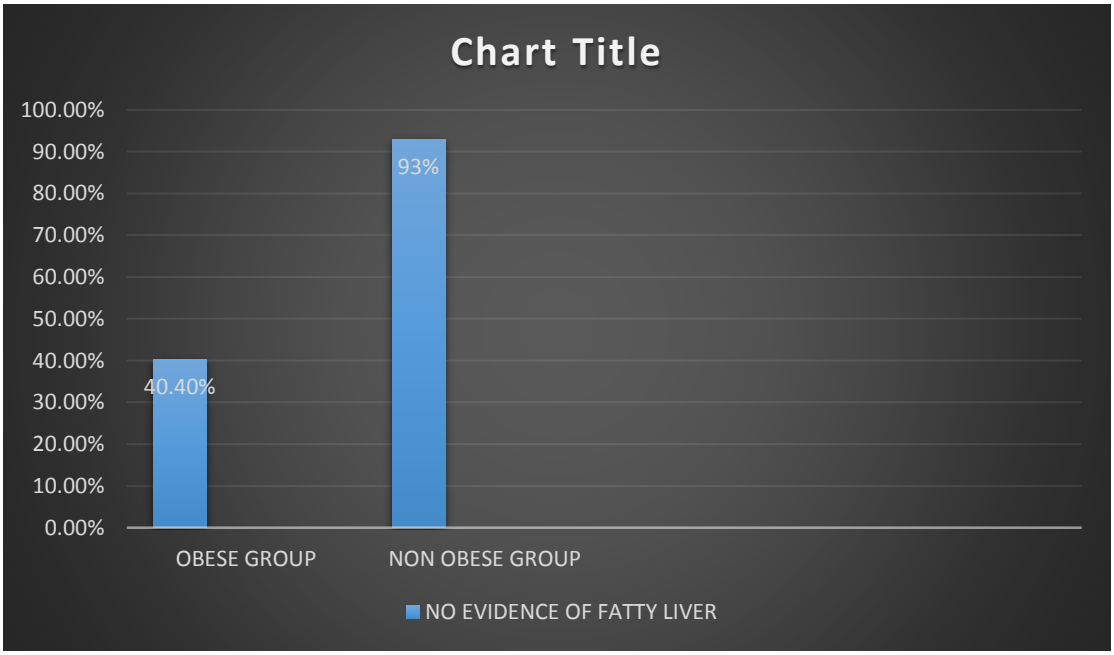


FIGURE 5:- PERCENTAGE OF STUDY POPULATION WITH HIGH, INTERMEDIATE AND LOW RISK IN OBESE GROUP.

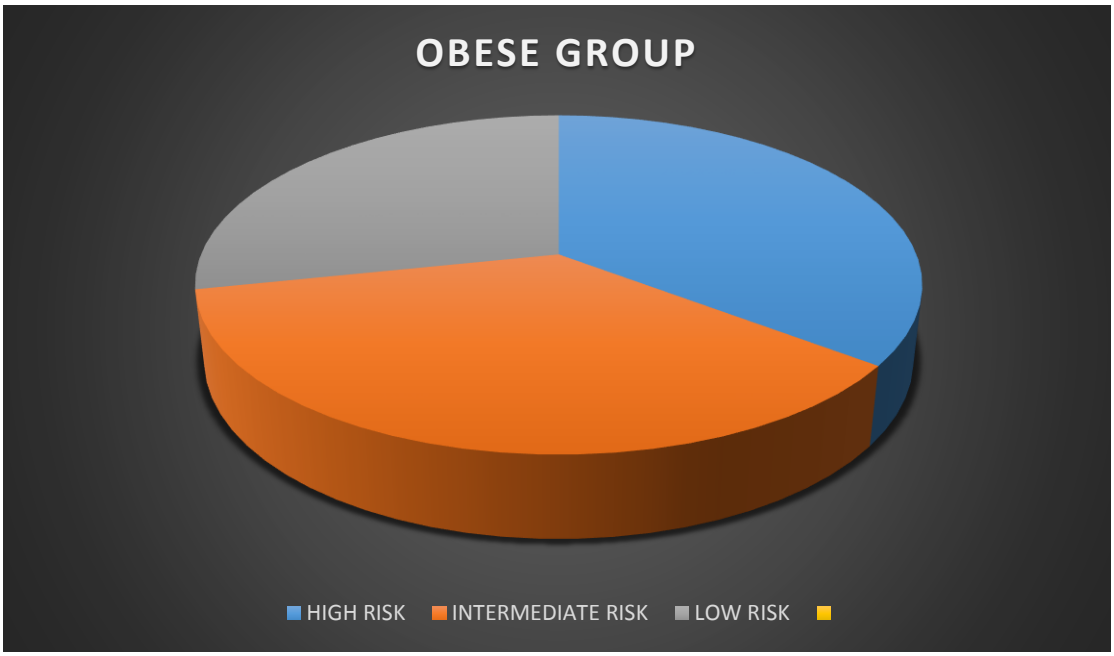
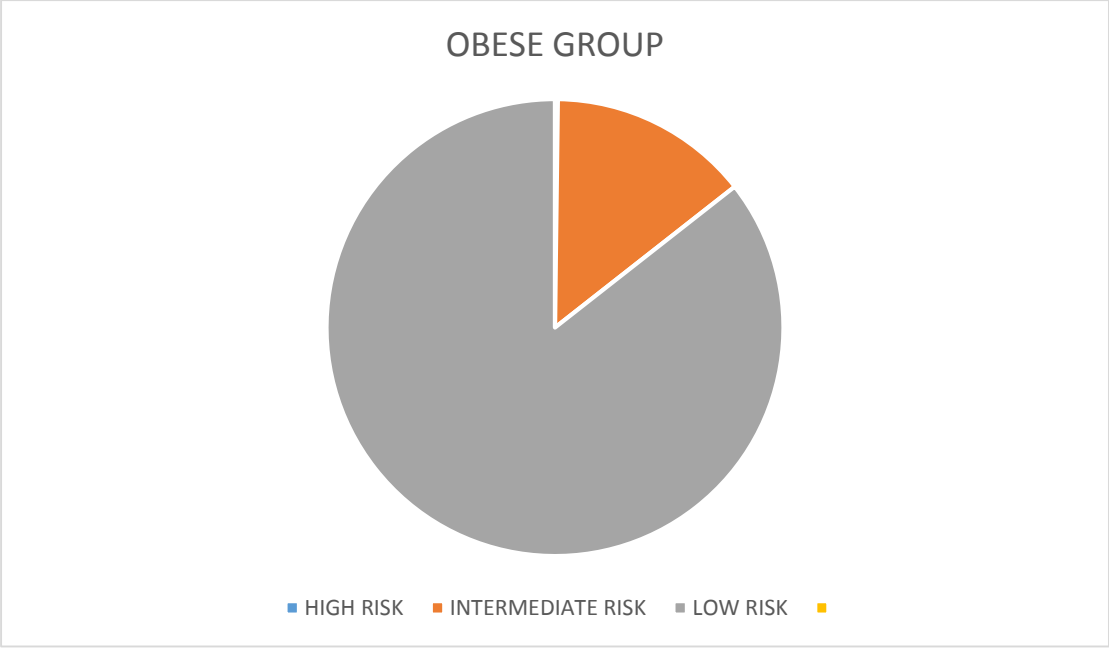


FIGURE 6 : STAGE OF FIBROSIS IN FIBRO SCAN IN OBESE GROUP.



DISCUSSION

6.DISCUSSION

The study was conducted in government stanley medical college hospital and the study population was 100 patients. Informed consent was obtained from all the patients included in the study.

All the patients included were Type 2 Diabetes Mellitus patients diagnosed by WHO criteria. Study population was subjected to blood investigations, ultrasonography and selected patients for fibro scan. The data was collected and interpreted and analysed using IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables.

The study population included 40 males and 60 females. Study population categorised to obese and non obese group. 57 % of population were in obese group and 43 % in non obese group. 59.6% of patients had ultrasonographic evidence of hepatic steatosis in obese group and 40.4% had no ultrasonographic evidence of hepatic steatosis in obese group.

6.9% of patients only had ultrasonographic evidence of hepatic steatosis in non obese group and 93% had no evidence of hepatic steatosis in non obese group. This shows the significance of body mass index and

obesity playing a major role in pathogenesis of non alcoholic fatty liver disease. The percentage of patients with fatty liver is significantly higher in obese group than in non obese group.

The non alcoholic fatty liver disease fibrosis score was calculated in all patients of study population and 35% of patients had high risk score in obese group compared to only 0.2% in non obese group.

36% of patients had intermediate risk in obese group compared to 13.9% in non obese group. 28% had low risk in obese group compared to 83.7% in non obese group.This showed that obese group had significantly higher risk of hepatic fibrosis compared to non obese group in diabetic patients.

When the patients of high risk NAFLD score of both groups including 20 patients from obese group and 1 patient from non obese group were subjected to fibro scan , the correlation between fibro scan and NAFLD score was similar and hence prove that non invasive tests have upcoming role in clinical practise compared to invasive tests like liver biopsy etc.. in early diagnosis and appropriate management for the group of patients with risk factors of non alcoholic fatty liver disease.

SUMMARY

7. SUMMARY

The study was done in 100 patients diagnosed to have Type 2 diabetes mellitus according to WHO criteria and categorised into obese and non obese groups according to Body Mass Index and ultrasonography was done to all subjects and categorised into patients with hepatic steatosis and no evidence of hepatic steatosis. Non alcoholic fatty liver disease fibrosis score was calculated for all patients and divided into three groups with low risk, intermediate and high risk.

Fibroscan was done for all patients with high risk NAFLD fibrosis score and correlation was studied, and all patients with high score was found to have significant stage of fibrosis according to METAVIR staging. Non alcoholic fatty liver disease fibrosis score was found significant in staging of hepatic fibrosis and correlated with fibro scan in staging of hepatic fibrosis or liver stiffness. NAFLD fibrosis score was found to be increased in obese patients, type 2 diabetes mellitus and helpful in early diagnosis of NAFLD and early intervention in reducing risk factors like hyperglycemia, hypertriglyceridemia, metabolic syndrome and reduce complications of NAFLD.

TABLES AND FIGURES

FIGURE 1: GENDER DISTRIBUTION IN STUDY POPULATION

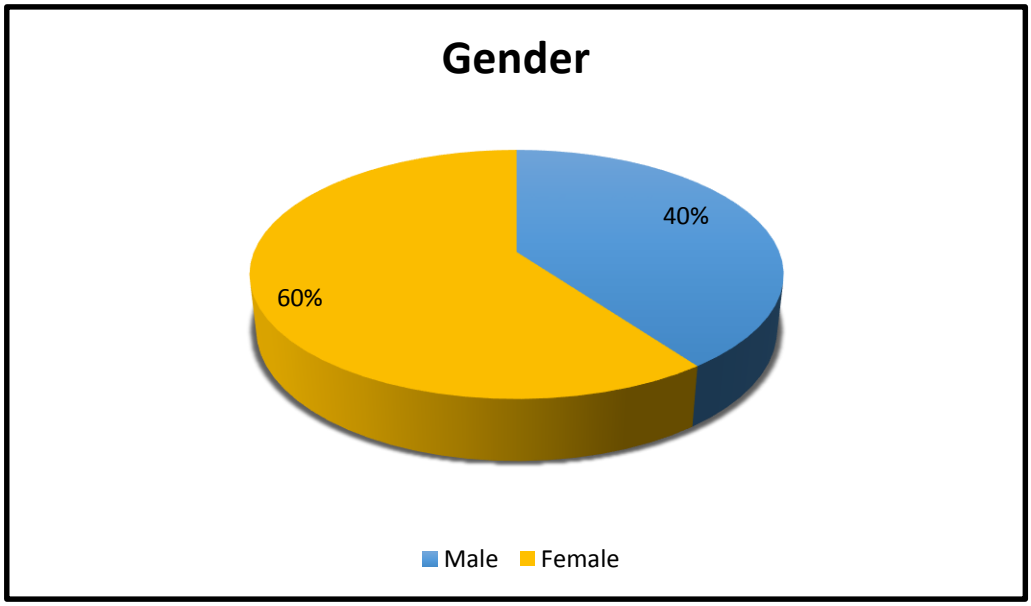


FIGURE 2: AGE RANGES IN THE STUDY POPULATION.

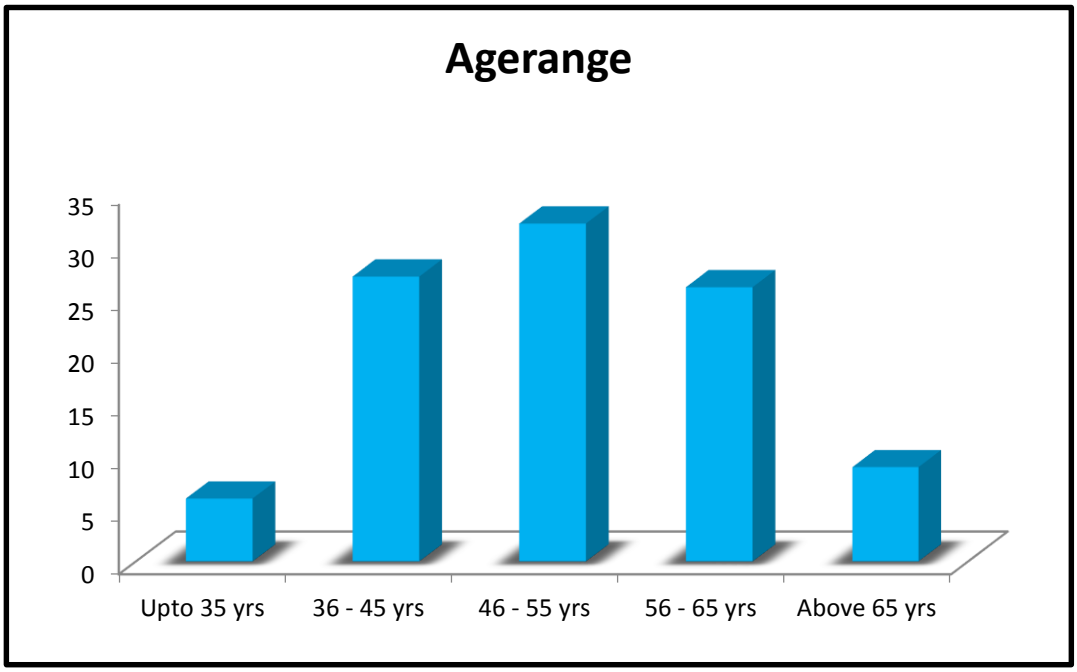


TABLE 1 : MEAN , MEDIAN AND MODE FOR AGE:

OBSERVATIONS	**TOTAL**	**MEAN**	**VARIANCE**	**STANDARD DEVATION**
100.00	5083.00	50.830	108.80	10.43
MINIMUM	25%	MEDIAN	MAXIMUM	MODE
26.000	44.000	50.000	74.000	45%

FIGURE 3: NAFLD FIBROSIS SCORE IN THE STUDY POPULATION

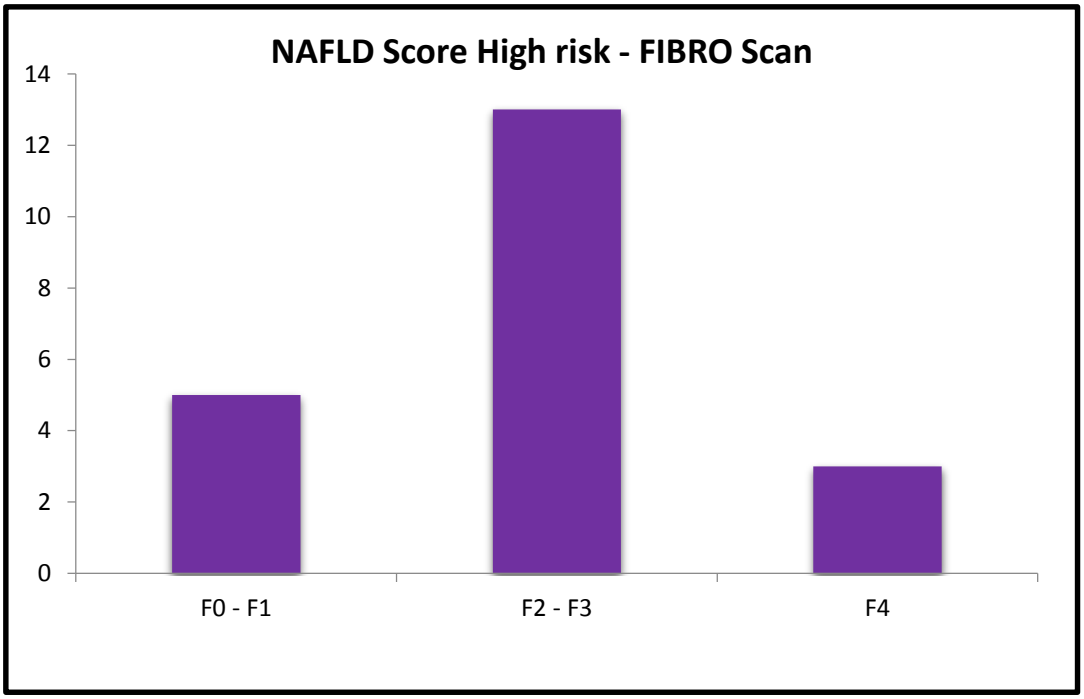


TABLE : 2 SEX DISTRIBUTION

SEX

	Frequency	Percent
Male	40	40.0
Female	60	60.0
Total	100	100.0

TABLE : 3: EVIDENCE OF FATTY LIVER IN OBESE AND NON OBESE GROUP.

	OBESE GROUP	**NON OBESE GROUP**
FATTY LIVER	**34 (59.6%)**	**3 (6.9%)**
NO EVIDENCE OF FATTY LIVER	**23(40.4%)**	**40 (93.1%)**
TOTAL	**57**	**43**

TABLE 4 : NAFLD SCORE IN OBESE AND NON OBESE GROUP

NAFLD SCORE	OBESE GROUP	NON OBESE GROUP
HIGH RISK	20 (35%)	1 (0.2%)
INTERMEDIATE RISK	21 (36 %)	6 (13.9%)
LOW RISK	16 (28%)	36 (83.7%)
TOTAL	57	43

TABLE : 5

	NAFLD SCORE			
AGE	**1**	**2**	**3**	**Total**
26	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**
28	**0**	**1**	**0**	**1**
Row%	**0.00%**	**100.00%**	**0.00%**	**100.00%**
Col%	**0.00%**	**4.00%**	**0.00%**	**1.00%**
29	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**
32	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**
33	**0**	**1**	**0**	**1**
Row%	**0.00%**	**100.00%**	**0.00%**	**100.00%**
Col%	**0.00%**	**4.00%**	**0.00%**	**1.00%**
35	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**

36	**0**	**1**	**1**	**2**
Row%	**0.00%**	**50.00%**	**50.00%**	**100.00%**
Col%	**0.00%**	**4.00%**	**1.85%**	**2.00%**
38	**1**	**0**	**1**	**2**
Row%	**50.00%**	**0.00%**	**50.00%**	**100.00%**
Col%	**4.76%**	**0.00%**	**1.85%**	**2.00%**
39	**1**	**0**	**1**	**2**
Row%	**50.00%**	**0.00%**	**50.00%**	**100.00%**
Col%	**4.76%**	**0.00%**	**1.85%**	**2.00%**
40	**2**	**2**	**1**	**5**
Row%	**40.00%**	**40.00%**	**20.00%**	**100.00%**
Col%	**9.52%**	**8.00%**	**1.85%**	**5.00%**
41	**0**	**1**	**3**	**4**
Row%	**0.00%**	**25.00%**	**75.00%**	**100.00%**
Col%	**0.00%**	**4.00%**	**5.56%**	**4.00%**
42	**1**	**0**	**0**	**1**
Row%	**100.00%**	**0.00%**	**0.00%**	**100.00%**
Col%	**4.76%**	**0.00%**	**0.00%**	**1.00%**
44	**1**	**2**	**2**	**5**
Row%	**20.00%**	**40.00%**	**40.00%**	**100.00%**
Col%	**4.76%**	**8.00%**	**3.70%**	**5.00%**

45	**2**	**2**	**2**	**6**
Row%	**33.33%**	**33.33%**	**33.33%**	**100.00%**
Col%	**9.52%**	**8.00%**	**3.70%**	**6.00%**
46	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**
47	**0**	**0**	**6**	**6**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**11.11%**	**6.00%**
48	**1**	**1**	**1**	**3**
Row%	**33.33%**	**33.33%**	**33.33%**	**100.00%**
Col%	**4.76%**	**4.00%**	**1.85%**	**3.00%**
49	**0**	**0**	**4**	**4**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**7.41%**	**4.00%**
50	**2**	**3**	**1**	**6**
Row%	**33.33%**	**50.00%**	**16.67%**	**100.00%**
Col%	**9.52%**	**12.00%**	**1.85%**	**6.00%**
51	**0**	**0**	**2**	**2**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**3.70%**	**2.00%**

52	**1**	**1**	**2**	**4**
Row%	**25.00%**	**25.00%**	**50.00%**	**100.00%**
Col%	**4.76%**	**4.00%**	**3.70%**	**4.00%**
53	**0**	**0**	**3**	**3**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**5.56%**	**3.00%**
54	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**
55	**0**	**2**	**0**	**2**
Row%	**0.00%**	**100.00%**	**0.00%**	**100.00%**
Col%	**0.00%**	**8.00%**	**0.00%**	**2.00%**
56	**1**	**1**	**2**	**4**
Row%	**25.00%**	**25.00%**	**50.00%**	**100.00%**
Col%	**4.76%**	**4.00%**	**3.70%**	**4.00%**
57	**1**	**0**	**1**	**2**
Row%	**50.00%**	**0.00%**	**50.00%**	**100.00%**
Col%	**4.76%**	**0.00%**	**1.85%**	**2.00%**
58	**2**	**0**	**2**	**4**
Row%	**50.00%**	**0.00%**	**50.00%**	**100.00%**
Col%	**9.52%**	**0.00%**	**3.70%**	**4.00%**

59	**2**	**1**	**1**	**4**
Row%	**50.00%**	**25.00%**	**25.00%**	**100.00%**
Col%	**9.52%**	**4.00%**	**1.85%**	**4.00%**
60	**0**	**2**	**3**	**5**
Row%	**0.00%**	**40.00%**	**60.00%**	**100.00%**
Col%	**0.00%**	**8.00%**	**5.56%**	**5.00%**
61	**2**	**0**	**1**	**3**
Row%	**66.67%**	**0.00%**	**33.33%**	**100.00%**
Col%	**9.52%**	**0.00%**	**1.85%**	**3.00%**
64	**0**	**0**	**2**	**2**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**3.70%**	**2.00%**
65	**0**	**1**	**1**	**2**
Row%	**0.00%**	**50.00%**	**50.00%**	**100.00%**
Col%	**0.00%**	**4.00%**	**1.85%**	**2.00%**
67	**0**	**1**	**0**	**1**
Row%	**0.00%**	**100.00%**	**0.00%**	**100.00%**
Col%	**0.00%**	**4.00%**	**0.00%**	**1.00%**
68	**0**	**0**	**2**	**2**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**

Col%	**0.00%**	**0.00%**	**3.70%**	**2.00%**
70	**1**	**1**	**1**	**3**
Row%	**33.33%**	**33.33%**	**33.33%**	**100.00%**
Col%	**4.76%**	**4.00%**	**1.85%**	**3.00%**
71	**0**	**1**	**0**	**1**
Row%	**0.00%**	**100.00%**	**0.00%**	**100.00%**
Col%	**0.00%**	**4.00%**	**0.00%**	**1.00%**
72	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**
74	**0**	**0**	**1**	**1**
Row%	**0.00%**	**0.00%**	**100.00%**	**100.00%**
Col%	**0.00%**	**0.00%**	**1.85%**	**1.00%**
TOTAL	**21**	**25**	**54**	**100**
Row%	**21.00%**	**25.00%**	**54.00%**	**100.00%**
Col%	**100.00%**	**100.00%**	**100.00%**	**100.00%**

FREQUENCY TABLES

TABLE : 6

	Frequency	Percent
Obese	57	57.0
Non Obese	43	43.0
Total	100	100.0

TABLE : 7

USG

	Frequency	Percent
Fatty Liver	37	37.0
Non Fatty liver	63	63.0
Total	100	100.0

FREQUENCY TABLES

TABLE : 8

NAFLD SCORE

	Frequency	Percent
High risk	21	21.0
Intermediate risk	25	25.0
Low risk	54	54.0
Total	100	100.0

TABLE : 9

FIBRO SCAN

	Frequency	Valid Percent
F0 - F1	5	23.8
F2 - F3	13	61.9
F4	3	14.3
Total	21	100.0
Total	100	

TABLE 10

NAFLD SCORE * FIBRO SCAN Crosstabulation

		FIBRO SCAN			Total
		F0 - F1	F2 - F3	F4	
NAFLD SCORE	High risk	5	13	3	21
Total		5	13	3	21

CONCLUSION

9.CONCLUSION

NAFLD is an increasingly important chronic liver disease next to alcoholic liver disease ranging from Steatosis,steatohepatitis to cirrhosis. Insulin resistance and oxidativestress play important roles in etiopathogenesis of non alcoholic liver disease. NAFLD is usually asymptomatic and incidentally diagnosed on routine laboratory investigation. Liver biopsy remains the most sensitive and specific means of providing prognostic information but nowadays other noninvasive tests are upcoming and playing a major role in clinical practise. In the absence of definite therapies, treatment is generally directed at optimizingbody weight and controlling risk factors. Liver transplantation is a therapeutic option for decompensated chronicliver disease.

ANNEXURE - I

MASTER CHART

MASTER CHART

S.NO	NAME	AGE	SEX	BMI	USG	NAFLD SCORE	FIBRO SCAN
1	Amutha	58	2	1	1	1	3
2	Sivagami	50	2	2	1	2	
3	Muniammal	50	2	1	2	2	
4	Shanthi	48	2	1	2	2	
5	Razia	47	2	2	2	3	
6	Bhagyam	61	2	1	1	1	2
7	Krishnaveni	60	2	2	2	3	
8	Sherifa	49	2	2	2	3	
9	Maheshwari	50	2	1	1	1	2
10	Kousia Begum	44	2	1	2	3	
11	Sujatha	38	2	2	2	3	
12	Beevi john	70	2	1	1	2	
13	Kala	35	2	2	2	3	
14	Elizabeth	40	2	1	1	1	2
15	Mani	60	1	1	2	3	
16	arumugam	70	1	2	1	1	1
17	narayanan	64	1	2	2	3	
18	shanmugam	60	1	1	1	2	
19	thiyagarajan	59	1	1	1	1	2
20	vasudevan	49	1	2	2	3	
21	robert	71	1	1	1	2	
22	bhoopalan	44	1	2	2	2	
23	srinivasan	61	1	1	1	1	2
24	pachiappan	45	1	2	2	3	
25	anand	49	1	1	2	3	
26	rajendiran	47	1	2	2	3	

27	Kuppu	40	2	1	1	1	2
28	suseela devi	58	2	2	2	3	
29	arun	28	1	1	1	2	
30	chinnaponnu	65	2	1	2	2	
31	nagaraj	39	1	1	1	1	2
32	krishnan	56	1	1	1	1	3
33	mahalakshmi	44	2	2	2	3	
34	ahmed	52	1	1	2	3	
35	vasanthi	53	2	2	2	3	
36	raman	44	1	1	1	2	
37	meenal	36	2	2	2	2	
38	selvi	47	2	2	2	3	
39	asirvatham	48	1	1	2	3	
40	balaraman	65	1	2	2	3	
41	logeshwari	39	2	2	2	3	
42	sarawathy	56	2	1	2	3	
43	vasuki	48	2	1	1	1	2
44	sukuna	51	2	1	2	3	
45	nagaraj	41	1	2	2	3	
46	selvam	50	1	2	2	3	
47	udaiyappan	41	1	1	1	2	
48	padmavathy	70	2	2	2	3	
49	rajeshwari	58	2	1	2	3	
50	valli	54	2	2	2	3	
51	kamalam	55	2	1	1	2	
52	selvi	47	2	2	2	3	
53	meenambal	60	2	2	2	2	
54	amudha	40	2	1	1	2	
55	mariammal	45	2	1	2	3	
56	devaki	52	2	2	2	3	
57	jothi	42	2	1	1	1	2
58	chellammal	61	2	2	2	3	

59	kuppuraj	49	1	2	2	3	
60	rajan	45	1	1	1	2	
61	kannan	51	1	1	2	3	
62	krishnamoorthy	57	1	1	1	1	2
63	mariappan	64	1	2	2	3	
64	janaki	68	2	2	2	3	
65	perumal	56	1	1	2	3	
66	damodharan	72	1	2	2	3	
67	deivanai	74	2	2	2	3	
68	sarasu	58	2	1	1	1	2
69	kothaiaamal	68	2	2	2	3	
70	nancy	33	2	1	2	2	
71	kayalvizhi	44	2	1	1	1	1
72	kaniappan	56	1	1	1	2	
73	nivedha	29	2	2	2	3	
74	divya	38	2	1	1	1	1
75	mohan	53	1	1	2	3	
76	monisha	26	2	2	2	3	
77	murugan	45	1	1	1	1	1
78	govindammal	45	2	1	1	2	
79	rosammal	59	2	1	1	2	
80	pappu	50	2	2	2	2	
81	krishnamoorthy	41	1	2	2	3	
82	devi	50	2	1	1	1	2
83	kannan	36	1	1	2	3	
84	valliyammal	53	2	2	2	3	
85	rajan	59	1	1	1	1	3
86	sumathy	40	2	1	2	3	
87	murali	47	1	2	2	3	
88	senthil	52	1	1	1	1	2

89	kanchana	45	2	1	1	1	1
90	priya	32	2	2	2	3	
91	ramasamy	40	1	1	1	2	
92	neelakandan	47	1	1	2	3	
93	joselin	41	2	1	2	3	
94	monica	55	2	2	1	2	
95	ayesha begum	67	2	1	2	2	
96	thamaraiselvi	60	2	1	2	3	
97	ramachandran	59	1	1	2	3	
98	ponni	46	2	2	2	3	
99	megala	52	2	1	1	2	
100	vimala	57	2	2	2	3	
			SEX	**BMI**	**USG**		**NAFLD SCORE**
			MALE-1	0BESE-1	FATTY LIVER-1		HIGH RISK-1
			FEMALE-2	NON-OBESE-2	NO FATTY LIVER-2		INTERMEDIATE RISK-2
							LOW RISK-3

ANNEXURE - II

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BIBLIOGRAPHY

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ANNEXURE - III

PROFORMA

PROFORMA

1. **NAME:**

2. **AGE:**

3. **SEX:**

4. **BMI:**

5. **DIABETES MELLITUS:**

6. **PLATELET COUNT:**

7. **ASPARTATE TRANSAMINASE:**

8. **ALANINE TRANSAMINASE:**

9. **SERUM ALBUMIN:**

10.FORMULA:

-1.675+ 0.037 * AGE (years) +0.094 * BMI (kg/m^2) +1.13 * IFG/ DIABETES (yes =1,no=0) +0.99 * AST/ALT ratio -0.013 * platelet (* 10^9 /l) -0.66 * albumin (g/dl).

10. ULTRASOUND:

FATTY LIVER- YES/NO

CONSENT FORM

STUDY TITLE :"NONALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE IN DIABETIC PATIENTS"

STUDY CENTRE : Govt.stanley medical college, Chennai-1

PARTICIPANT NAME : **AGE:** **SEX**: **IP/OP NO:**

I confirm that I have understood the purpose of procedure for the above study, I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I understand that the investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties of published, unless as required under the law. I agree not to restrict the use of any results that arise from the study.

I hereby consent to participate in this study of **:"NONALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE IN DIABETIC PATIENTS"**

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Signature of Investigator: Place :

Date :

Study Investigators Name Institution

Signature / Thumb Impression of patient